

FENOFIBRATE 145 mg

SmPC

Clean version – May 2007

SUMMARY OF PRODUCT CHARACTERISTICS

LIPIDIL 145 ONE XAFENOR 145 MG LIPERIAL 145 MG

(Tradename approved in the RMS = Germany)

1. NAME OF THE MEDICINAL PRODUCT

<Tradename> 145 mg, Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 145.0 mg fenofibrate (nanoparticles).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

White, oblong, film-coated tablets engraved “145” on one side and “Fournier logo” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypercholesterolaemia and hypertriglyceridaemia alone or combined (types IIa, IIb, IV dyslipidaemias, as well as types III and V dyslipidaemias) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk such as hypertension and smoking.

The treatment of secondary hyperlipoproteinaemias is indicated if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).

Appropriate dietary measures initiated before therapy should be continued.

4.2. Posology and method of administration

In combination with diet, this medicinal product constitutes a long-term treatment, the efficacy of which should be monitored periodically.

Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-C, triglycerides). If an adequate response has not been achieved after several months (e.g. 3 months), complementary or different therapeutic measures should be considered

Posology:

Adults: The recommended dose is one tablet containing 145 mg fenofibrate taken once daily. Patients currently taking one 200mg capsule or one 160 mg tablet can be changed to one 145 mg fenofibrate tablet without further dose adjustment.

Elderly patients: In elderly patients, the usual adult dose is recommended.

Patients with renal impairment: Dosage reduction is required in patients with renal impairment. The use of dosage forms containing a lower dose of active ingredient (100 mg or 67 mg fenofibrate) is recommended in these patients.

Children: The use of the 145 mg dosage form is contraindicated in children.

Hepatic disease: Patients with hepatic disease have not been studied.

Method of administration: Tablet should be swallowed whole with a glass of water.

<Tradename> 145 mg, Film-coated tablet may be given at any time of the day, with or without food (see section 5.2.).

4.3. Contraindications

hepatic insufficiency (including biliary cirrhosis),

renal insufficiency,

children,

hypersensitivity to fenofibrate or any component of this medication,

known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen,

gallbladder disease,

chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia.

Use during pregnancy and lactation: see section 4.6.

<Tradename> 145 mg, Film-coated tablet should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions. See section 4.4.

4.4. Special warnings and precautions for use

Secondary cause of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is initiated.

For hyperlipidaemic patients taking estrogens or contraceptives containing oestrogens it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

Liver function: As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. Patients with hypoalbuminemia and renal insufficiency in their personal history have a higher incidence of myotoxicity. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the upper normal range). In such cases treatment with fenofibrate should be stopped.

Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, hypoalbuminaemia, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor (statins), especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity.

Renal function: Treatment should be interrupted in case of an increase in creatinine levels > 50% and ULN (upper limit of normal). It is recommended that creatinine measurement may be considered during the first three months after initiation of treatment.

This medicinal product contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

<Tradename> 145 mg, Film-coated tablet should not be taken in patients allergic to soya lecithin or related products due to the risk of hypersensitivity reactions (see section 4.3).

4.5. Interactions with other medicinal products and other forms of interaction

Oral anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. Therefore, this combination is not recommended.

Cyclosporin: Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates: The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with HMG-CoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity (see section 4.4).

Cytochrome P450 enzymes: *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

4.6. Pregnancy and lactation

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, <Tradename> 145 mg, Film-coated tablet should only be used during pregnancy after a careful benefit/risk assessment

There are no data on the excretion of fenofibrate and/or its metabolites into breast milk. Consequently, <Tradename> 145 mg, Film-coated tablet should not be used in nursing mother

4.7. Effects on the ability to drive and use machines

<Tradename> 145 mg, Film-coated tablet has no influence on the ability to drive and use machines.

4.8. Undesirable effects

The frequencies of adverse events are ranked according to the following: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Gastrointestinal disorders:

Common: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity

Uncommon : Pancreatitis *

Hepato-biliary disorders:

Common: Moderately elevated levels of serum transaminases (see Special precautions for use)

Uncommon: Development of gallstones

Very rare: episodes of hepatitis. When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable (see Special warnings)

Skin and subcutaneous tissue disorders:

Uncommon: rashes, pruritus, urticaria or photosensitivity reactions

Rare: alopecia

Very rare: cutaneous photosensitivity with erythema, vesiculation or nodulation on parts of the skin exposed to sunlight or artificial UV light (e.g. sunlamp) in individual cases (even after many months of uncomplicated use)

Musculoskeletal, connective tissue and bone disorders:

Rare: diffuse myalgia, myositis, muscular cramps and weakness

Very rare: rhabdomyolysis

Cardiovascular system

Uncommon: Thromboembolism (pulmonary embolism, deep vein thrombosis)*.

Blood and lymphatic system disorders:

Rare: decrease in haemoglobin and leukocytes

Nervous system disorders:

Rare: sexual asthenia, headache

Respiratory, thoracic and mediastinal disorders:

Very rare: interstitial pneumopathies

Investigation:

Uncommon: Increases in serum creatinine and urea.

* In the FIELD-study, a randomized placebo-controlled trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; $p = 0.031$). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; $p = 0.022$) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0 % [48/4900 patients] versus fenofibrate 1.4% [67/4895 patients]; $p = 0.074$).

4.9. Overdose

No case of overdose has been reported. No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.

ATC code: C10 AB 05

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPAR α).

Through activation of PPAR α , fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPAR α also induces an increase in the synthesis of apoproteins AI and AII.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII.

In addition, through modulation of the synthesis and the catabolism of VLDL fractions fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk.

Because of its effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus. At the present time, no results of long-term controlled clinical trials are available to demonstrate the efficacy of fenofibrate in the primary or secondary prevention of atherosclerotic complications.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

5.2. Pharmacokinetic properties

<Tradename> 145 mg, Film-coated tablet contains 145 mg of fenofibrate nanoparticles.

Absorption: Maximum plasma concentrations (C_{max}) occur within 2 to 4 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

Contrarily to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticle formulation is independent from food intake. Therefore, <Tradename> 145 mg, Film-coated tablet may be taken without regard to meals.

A food-effect study involving administration of the new 145 mg tablet formulation of fenofibrate to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_{max}) to fenofibric acid is not affected by food.

Distribution: Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Metabolism and excretion: After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

The plasma elimination half-life of fenofibric acid is approximately 20 hours.

5.3. Preclinical safety data

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses. No sign of any effect on fertility has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Sucrose

Lactose monohydrate,

Silicified microcrystalline cellulose,

Crospovidone,

Hypromellose,

Sodium lauril sulfate

Docusate sodium

Magnesium stearate.

Coating:

Polyvinyl alcohol,

Titanium dioxide (E171),

Talc,

Soybean lecithin,

Xanthan gum.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

3 years

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

Thermoformed blister strips (clear PVC/PE/PVDC sealed with aluminium complex) of 10 or 14 tablets each.

Boxes of 10, 20, 28, 30, 50, 84, 90, 98 and 100 tablets.

Hospital pack sizes: 280 (10 x 28) and 300 (10 x 30) tablets.

Not all pack sizes may be marketed.

6.6. Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

As appropriate nationally.

8. MARKETING AUTHORISATION NUMBER

As appropriate nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

May 2007.